The effect of race on longitudinal maternal central hemodynamics

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Contribution:

What are the novel findings of this work?

In pregnancy, White, compared to Black and Asian women, achieve higher cardiac output and lower peripheral vascular resistance. White women increase stroke volume and heart rate; Black and Asian women increase heart rate with decreased stroke volume.

What are the clinical implications of this work?

Race-specific differences in hemodynamic adaptation to pregnancy should be considered in future studies examining the relationship between cardiovascular changes and pregnancy complications and on a clinical basis, a lower threshold for hemodynamic assessment during pregnancy should exist for women of Black or Asian origin if they demonstrate cardiovascular decompensation.

Abstract

Objective: To compare maternal central hemodynamics between White, Black and Asian women.

Methods: This was a prospective, longitudinal study of maternal central hemodynamics by a bioreactance method at 11^{+0}-13^{+6}, 19^{+0}-24^{+0}, 30^{+0}-34^{+0} and 35^{+0}-37^{+0} weeks' gestation, in White (n=1165), Black (n=247) and Asian (n=116) women. Multilevel linear mixed-effects analysis was performed to compare the repeated measures of the cardiac variables controlling for maternal characteristics and medical history.

Results: Cardiac output (CO) increased with gestational age to a peak at 32 weeks; the highest CO was in White women and the lowest in Asian women. Stroke volume (SV) increased with gestation in White women, decreased in Black women and remained static in Asian women. Heart rate (HR) increased with gestation to 32 weeks and then remained constant; HR was highest in Black women and lowest in White women. Peripheral vascular resistance (PVR) showed a reversed pattern to CO; the highest values were in Asian women and the lowest in White women. The least favourable hemodynamic profile in Black and Asian, compared to White women was reflected in the higher rates of small for gestational age infants.

Conclusion: There are race-specific differences in maternal cardiac adaptation in pregnancy. White women have the most favourable cardiac adaptation by increasing SV and HR, achieving the highest CO and lowest PVR. In contrast, Black and Asian, compared to White women, have lower CO and higher PVR, increasing their CO through a rise in HR due to a declining or static SV.

INTRODUCTION

Pregnancy represents a model of volume and pressure overload which result in significant alterations of the cardiac geometry and function. Optimal maternal cardiac adaptation results in increased blood volume and left ventricular (LV) mass with a concomitant increase in cardiac output (CO), stroke volume (SV) and heart rate (HR), along with decreased peripheral vascular resistance (PVR).[1] Failure to achieve an increase in CO and decrease in PVR has been associated with the development of preeclampsia (PE) and birth of small for gestational age (SGA) neonates.[2-4]

There is extensive evidence of racial disparity in the risks of adverse pregnancy outcomes and long-term development of cardiovascular diseases. In Black and Asian pregnant women, compared to White women, there is increased risk of miscarriage, stillbirth, PE, SGA and gestational diabetes mellitus (GDM).[5] Outside pregnancy, Black populations have higher incidence of hypertension,[6] Type 2 diabetes,[6] end stage renal failure[7] and mortality from stroke,[8, 9] whilst Asians have increased risk of diabetes and mortality from coronary artery disease.[10] In non-pregnant individuals there are racial differences in cardiovascular function at rest and during exercise and poorer reserve in Black and Asian populations compared to Whites.[11-14]

The objective of this study is to ascertain the impact of race on maternal cardiac adaptation in pregnancy.

METHODS

Study population

This was a prospective, longitudinal study assessing maternal central hemodynamics in women with singleton pregnancies attending for routine care in six maternity hospitals in the UK between November 2015 and May 2016. The study was carried out in some of the hospitals participating in an international multicentre study involving routine screening for PE by maternal factors and biomarkers at 11^{+0} to 13^{+6} week's gestation; [15] those identified as being at high-risk were invited to participate in the ASPRE trial of aspirin versus placebo.[16] The study was approved by the NHS Research Ethics Committee (REC reference: 13/LO/1479).

We recorded maternal demographic characteristics and medical history and performed hemodynamic studies at 11^{+0} to 13^{+6}, 19^{+0} to 24^{+0}, 30^{+0} to 34^{+0} and 35^{+0} to 37^{+0} weeks' gestation.

Maternal factors

Maternal factors recorded included maternal age, height, weight at each visit, self-reported racial origin (White, Black and Asian), method of conception (spontaneous or use of artificial reproductive technologies), cigarette smoking during pregnancy, medical history, medications, parity and obstetric history (nulliparous, multiparous with and without previous PE and or SGA).

Assessment of maternal cardiovascular function

Maternal cardiac function was assessed using a non-invasive, bioreactance method (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK) validated both in pregnant and non-pregnant populations.[4, 17, 18] When an alternating electrical current traverse the thoracic cavity, the bioreactance technology uses the simultaneous relative phase shifts to calculate stroke volume. After 15 minutes of rest, four dual-surface electrodes were applied across the maternal back and cardiac variables [CO, SV, HR, peripheral vascular resistance (PVR) and mean arterial pressure (MAP)] were recorded in a sitting position for 10 minutes at 30-second intervals (20 cycles). The averages of the final 10 cycles of hemodynamic variables were included in the analysis.

Outcome measures

The outcome measure was the effect of maternal racial origin on longitudinal changes of CO, SV, HR, PVR and MAP with advancing gestational age.

Inclusion and exclusion criteria

The inclusion criteria were White, Black and Asian racial origin, singleton pregnancies resulting in the birth of morphologically normal livebirths or stillbirths at or after 24 weeks' gestation and attendance for hemodynamic studies for at least three of the four visits. Exclusion criteria were maternal age <18 years, mixed racial origin, pre-existing maternal cardiac conditions, fetal abnormalities, incomplete follow-up and termination of pregnancy or miscarriage.

Definitions of adverse pregnancy outcomes

The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy.[19] Diagnosis of SGA neonates and large for gestational age (LGA) neonates were based on the finding of birthweight <10th percentile and >90th percentile, respectively, of the Fetal Medicine Foundation reference range for gestational age.[20] Neonatal morbidity was defined by the presence of any one of respiratory distress syndrome, intrapartum sepsis, necrotizing enterocolitis or neonatal hypoglycemia.

Statistical analysis

Maternal demographic characteristics, medical history and pregnancy outcomes between racial groups were compared using the chi-square test or Fisher's exact test for categorical variables. Normality of the distribution of numerical data was assessed with the Kolmogorov – Smirnov test. As the data were not normally distributed, the distribution of maternal weight, CO, SV, MAP and PVR were made Gaussian after $\log_{10}$ transformation. The Kruskal-Wallis test with post hoc analysis was used to compare continuous data. Data are presented as median (interquartile range) for continuous variables and as n (%) for categorical variables. For the repeated measures analysis of the maternal hemodynamic variables multilevel linear mixed-effects analysis was performed, controlling for time (the four visits) and factors among maternal demographic characteristics, past medical history and medication use, which are known to affect these measurements.[21, 22] The fixed-effect component included time, race (White, Black, and Asian), maternal age, $\log_{10}$ weight, height, parity (nulliparous, multiparous with and without previous PE or SGA), spontaneous conception, smoking, family history

of PE, medical co-morbidities including chronic hypertension, autoimmune disease, asthma, diabetes mellitus type I and type II, medication use (labetalol, nifedipine/methyldopa, prednisolone, aspirin) and first-order interaction between racial group and time. The likelihood radio (LR) test was used to define the best multilevel model (including only the random slope for time or random intercept versus including both the random intercept and slope) and to compare it with the base-model (with no random effects). The fixed and random effects of the multilevel models and the estimated marginal means at the four visits are presented.

The software program IBM SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis (IBM Corp, Released 2015, IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp).

RESULTS

Study population

We recruited 2,024 women to the hemodynamic studies, but 450 were excluded from analysis because the pregnancies ended in miscarriage or termination (n=27), the women attended for less than three of the four visits (n=384), or there was loss to follow up (n=39). We also excluded women of mixed race (n=46) due to small numbers. The study population included 1165, 247 and 116 White, Black and Asian women, respectively. The maternal characteristics and pregnancy outcomes for the three groups at the screening visit are shown and compared in Table 1.

A higher proportion of Black and Asian, compared to White women, were screen positive for PE and participated in the ASPRE trial, but there were no significant differences between the racial groups in the proportion of women allocated to the aspirin than placebo arm of the trial. Black women were heavier and taller than White women, whilst Asian women were shorter and lighter. The incidence of smoking was lower in Asian and Black than White women. There was higher proportion of nulliparous women in the White group and more multiparous women with history of PE or SGA in the Black group. The incidence of chronic hypertension, diabetes mellitus and treatment with anti-hypertensives was higher in Black than White women. Women of Black and Asian origins, compared to White women, delivered babies with lower birthweight. Despite a higher incidence of gestational diabetes mellitus (GDM) in Asian compared to White women, the former group delivered the smallest infants. On the contrary, the rate of macrosomia was highest in White women despite higher proportion of nulliparous women and lowest incidence of GDM. There were no differences in rates of PE, emergency caesarean section, rates of neonatal unit admissions and neonatal morbidities in the three groups.

Multilevel linear mixed-effects models

The fixed and random effects of the best multilevel models are illustrated in Figure 1. Data on estimated marginal means for all hemodynamic variables are given in Table 2 and data on fixed and random effects of multilevel models for CO, HR and SV are given in Table S1 and for MAP and PVR are given in Table S2.

Maternal demographic characteristics medical history

Increasing maternal age was associated with a decrease in Log_{10} CO, HR and higher Log_{10} PVR. Increasing maternal height was associated with higher Log_{10} CO, Log_{10} SV and lower HR and Log_{10} PVR. Maternal Log_{10} weight was associated with higher Log_{10} CO, Log_{10} SV, HR and Log_{10} MAP. Smoking was associated with lower Log_{10} MAP and multiparous women (irrespective of previous PE or SGA) compared to nulliparous had higher Log_{10} CO, HR and lower Log_{10} PVR.

Maternal chronic hypertension was associated with higher Log_{10} MAP and use of labetalol, nifedipine or methyldopa was associated with higher Log_{10} MAP and higher Log_{10} PVR. Use of prednisolone was associated with higher Log_{10} SV and use of aspirin or placebo, compared to no treatment with higher Log_{10} MAP. Autoimmune disease was associated with lower Log_{10} CO and higher Log_{10} PVR.

There was no significant contribution in any of the models from spontaneous conception, family history of PE, asthma, diabetes mellitus Type I,II. There was significant interaction between racial group and time for all the cardiac variables.

Changes with time after controlling for maternal characteristics

Log_{10} CO in all three racial groups increased during the first three visits and declined in the fourth. Black women had consistently lower Log_{10} CO than White women after the first visit, and Asian women had lower Log_{10} CO than White women throughout pregnancy.

Log_{10} SV in White women increased after the first visit, but subsequently declined. In Black women, compared to White women, Log_{10} SV in the first visit was the same but in subsequent visits it was lower. In Asian women Log_{10} SV was lower than in White women and it did not change significantly with gestational age.

HR in all three racial groups shared similar incremental trends until the third visit with a plateau after that. In Black women HR was higher than in White women in all four visits. In Asian women was not significantly different than in either White or Black women in any of the visits.

Log_{10} PVR and Log_{10} MAP in all three racial groups decreased between the first and third visits and subsequently increased. Log_{10} PVR in Asian women was higher than in White and Black women in all four visits.

Log_{10} MAP in Black and Asian women was lower than in White women in all four visits.

DISCUSSION

Main findings

The results of this study have demonstrated that, after adjusting for maternal demographic characteristics and medical history, there are significant differences in cardiac adaptation in pregnancy between women of White, Black and Asian racial origin. In all three racial groups there was an increase in CO with gestational age which peaked at 32 weeks' gestation and subsequently declined at 35-37 weeks; however, CO was higher in White than in Black and Asian women. More importantly, the mechanisms by which the women achieved the increased CO differed according to race; White women increased their CO by increasing both SV and HR. On the contrary, Black and Asian women increased their CO primarily by increasing their HR, following a decline or a static SV in Black and Asian woman, respectively. All three groups demonstrated the expected decrease in PVR with gestation, with Asian women having persistently highest PVR followed by Black and then White women with the lowest PVR.

Comparison of findings to those of previous studies

Pregnancy represents an excellent model of physiological adaptation to volume overload, comparable to that in trained endurance athletes such as swimmers or runners.[23] Compared to untrained individuals, after indexing for body surface area, endurance athlete's central hemodynamics at rest, show increased LV mass, LV end diastolic dimension and SV with reduced HR[24-27] and normal diastolic and systolic function[14] with no difference in the resting CO, PVR and BP.[25] Their hearts undergo

eccentric hypertrophy (large dilated cavities and relatively thin walls). These changes are suggestive of a modulation of the hemodynamic profile to more efficient one, basing oxygen transport on SV rather than HR. An efficient energy management system avoids high resting HR because this shortens diastole in each cardiac cycle, and results in reduction of myocardial and coronary perfusion time,[28] impaired ventricular filling,[28] and increased myocardial oxygen demand.[28] In normal pregnancy, similar changes in LV dimensions such as those seen in athletes have been reported, and the adaptation is efficient since in the first two trimesters the increase in CO is due to 40% increase in SV and only a 10% increase in HR.[1]

Previous studies on maternal cardiovascular adaptation in pregnancy have either not reported the distribution of women from different racial groups or they did not report separately the results of the different racial groups. In contrast, studies in non-pregnant populations have reported clear racial differences in cardiovascular risk and hemodynamic adaptation to cardiovascular stress. Asians, compared to Whites, have a two-fold increase in the risk of coronary artery disease with a concomitant higher risk of death from cardiovascular disease.[10] Hemodynamic studies reported that in Asians at rest, after adjustment for body surface area, the HR is 10% higher and SV is 28% lower than in Whites.[29] A population study of 30,000 subjects in London reported that Asians, compared to Whites, had impaired longitudinal LV function, greater LV filling pressure and higher rates of concentric remodelling (hearts with thick walls and relatively small cavities) independent of other demographic and clinical parameters.[30] People of African ancestry have a four-fold increase in risk of hypertension than White populations and a

higher risk of mortality associated with stroke.[6] Population studies comparing Black to White cohorts at rest, demonstrated that the former had greater LV thickness for equivalent levels of blood pressure and prevalence of concentric hypertrophy,[31] higher PVR and lower CO, controlling for body surface area.[32] Furthermore, Black, compared to White athletes, show a disproportionate increase with training in LV mass for a given LV volume, indicating attenuated myocardial relaxation and LV filling. [33] It is therefore possible that Black and Asian women, by comparison with White women, enter pregnancy with a less favourable cardiovascular reserve and worse potential to cope with hemodynamic stress.

Implications for clinical studies

Women of Black or Asian race have been shown to have higher rates of SGA compared to White women. [5, 34] Women who deliver SGA babies have been shown to have impaired cardiovascular adaptation in pregnancy. Stott *et al*, studied longitudinal cardiac adaptation in 84 high risk women due to previous HDP or chronic hypertension and found that women who delivered babies with birthweight <10th percentile have static or suppressed CO and SV with persistently raised PVR, with a trend of higher HR.[4] This characteristic hemodynamic trend further corroborated other studies which showed that pregnancies with failed volume response, manifested in suppressed SV, are destined to develop SGA.[4, 35, 36] In our study the hemodynamic adaptation of Black and Asian women was characterised by a similar low-volume high-resistance state and this was reflected in the considerably higher prevalence of SGA neonates in Black and Asian women than in White women. Furthermore, the worse hemodynamic profiles of Black

and Asian women were reflected by the fact that a higher proportion of them were screened positive in the APSRE trial, which further corroborated our previous study which demonstrated that women who screened high-risk for preterm PE have impaired cardiovascular adaptation, irrespective of pregnancy outcomes.[37]

Strengths and limitations

Strengths of our study include, first, examination of the impact of race on maternal central hemodynamics during pregnancy, which was not reported in previous studies identified by search of PubMed and EMBASE, second, longitudinal collection of data from a large number of women in each racial group, and third, adjustment of hemodynamic indices for maternal demographic characteristics and medical history. A limitation of the study is participation of some of our patients in the ASPRE trial on aspirin vs. placebo. It was for this reason that in the mixed model analysis we controlled for the use of aspirin, which was not shown to be a significant predictor of maternal hemodynamic variables. An additional limitation is that we have not controlled for socioeconomic status, which in non-pregnant populations has been shown to explain to a large extent the differences in adult mortality across different races.[38, 39] However, we think that this unavoidable limitation represents a reality in everyday clinical practice that cannot be modified during pregnancy.

Conclusions

We found race-specific differences in hemodynamic adaptation to pregnancy. Such differences should be considered in future studies examining the relationship between

cardiovascular changes and pregnancy complications and on a clinical basis, a lower threshold for hemodynamic assessment during pregnancy should exist for women of Black or Asian origin if they demonstrate signs or symptoms of cardiovascular decompensation.

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Figure legend

Figure 1. Linear mixed-effects model for maternal hemodynamics in the four visits after controlling for demographic characteristics, past medical history and medications in White (blue line), Black (red line) and Asian (green line).

Table 1. Demographic characteristics and pregnancy outcome in the three racial groups.

	White (n=1165)	Black (n=247)	Asian (n=116)
Age in years, mean (SD)	30.9 (5.3)	31.4 (5.7)	31.6 (5.3)
Weight at booking in kg, median (IQR)	67.9 (60.4, 79.1)	77.9 (67.6, 90.4) ***	61.4 (54.3, 69.7) ***$^{+++}$
Height in cm, mean (SD)	165.1 (6.3)	165.4 (6.8) ***	158.6 (5.5) *** $^{+++}$
Smoking, n (%)	82 (7)	5 (2) **	1 (0.9) **
Family history of PE (%)	77 (6.6)	16 (6.5)	2 (1.7) *
Spontaneous conception, n (%)	1124 (96.5)	245 (99.2) *	113 (97.4)
Nulliparous, n (%)	642 (55.1)	109 (44.1) **	59 (50.9)
Parous with previous PE or FGR, n (%)	67 (5.8)	28 (11.3) **	10 (8.6)
Chronic hypertension, n (%)	13 (1.1)	16 (6.5) ***	2 (1.7)
Asthma, n (%)	17 (1.5)	7 (2.8)	1 (0.9)
Pre-existing diabetes, n (%)	4 (0.3)	4 (1.6) **	1 (0.9)
Autoimmune disease, n (%)	8 (0.7)	0 (0.0)	1 (0.9)
Labetalol, n (%)	52 (4.5)	28 (11.3) *** $^{++}$	4 (3.4)
Nifedipine or Methyldopa, n (%)	12 (1.0)	8 (3.2) **	3 (2.6)
ASPRE trial placebo group, n (%)	128 (11.0)	67 (27.1) ***	21 (18.1) *
ASPRE trial aspirin group, n (%)	122 (10.5)	64 (25.9) ***	19 (16.4) $^{+}$
Prednisolone, n (%)	2 (0.2)	1 (0.4)	0 (0.0)
Pregnancy outcome			
- Preeclampsia, n (%)	36 (3.1)	12 (4.9)	3 (2.6)
- Gestational hypertension, n (%)	42 (3.6)	14 (5.7)	3 (2.6)
- Gestational diabetes, n (%)	45 (3.9)	16 (6.5)	12 (10.3) **
- Birth < 37 weeks gestation, n (%)	41 (3.5)	10 (4.0)	3 (2.6)
- Induction of labor, n (%)	364 (31.2)	72 (29.1)	35 (30.2)
- Emergency cesarean, n (%)	192 (16.5)	47 (19.0)	20 (17.2)
- Operative birth for fetal distress, n (%)	143 (12.3)	33 (13.4)	12 (10.3)
- Gestational age at birth in w, median (IQR)	40.0 (39.0-40.9)	39.6 (38.9-40.6) **	39.6 (38.6-40.3) **
Neonatal outcome			
- Birth-weight in g, mean (SD)	3425 (540)	3232 (536) ***	3153 (499) ***
- Birth weight z-score, mean (SD)	-0.020 (1.08)	-0.407 (1.07) ***	-0.613 (1.17) ***
- Birth weight percentile, median (IQR)	51.9 (23.7, 76.7)	32.9 (14.2, 62.8) ***	24.6 (10.9, 53.3)
- Birth weight <10th centile, n (%)	146 (12.5)	44 (17.8) *	28 (24.1) **
Perinatal mortality, n (%)	4 (0.4)	1 (0.4)	0 (0.0)

Neonatal unit admission, n (%)	68 (5.8)	9 (3.6)	8 (6.9)
Neonatal morbidity[a], n (%)	57 (4.9)	8 (3.2)	5 (3.4)

a = includes respiratory distress syndrome, need for ventilation, intrapartum sepsis, necrotizing enterocolitis, neonatal hypoglycemia

Compared to White: *p<0.05, ** p<0.01, ***p<0.001;

Compared to Black: + p<0.05, ++ p<0.01, +++ p<0.001

Table 2. Multilevel linear mixed-effects models for maternal hemodynamic variables: estimated marginal means with 95% confidence intervals.

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
Log_{10} Cardiac output				
White	0.727 (0.701-0.754)	0.758 (0.732-0.785)	0.768 (0.741-0.795)	0.757 (0.730-0.784)
Black	0.732 (0.703-0.761)	0.733 ** (0.704-0.763)	0.750 * (0.721-0.779)	0.737 ** (0.708-0.767)
Asian	0.698 ** ++ (0.665-0.730)	0.713 *** (0.680-0.745)	0.729 *** (0.697-0.761)	0.723 ** (0.691-0.755)
Log_{10} Stroke volume				
White	1.876 (1.833-1.919)	1.894 (1.851-1.937)	1.881 (1.838-1.924)	1.871 (1.828-1.914)
Black	1.875 (1.831-1.920)	1.851 *** (1.807-1.896)	1.848 *** (1.804-1.892)	1.840 *** (1.795-1.884)
Asian	1.844 ** + (1.797-1.892)	1.837 *** (1.790-1.884)	1.837 *** (1.790-1.884)	1.829 *** (1.782-1.876)
Heart Rate				
White	81.754 (75.339-88.169)	84.432 (78.017-90.847)	88.976 (82.558-95.395)	88.944 (82.524-95.365)
Black	82.908 (76.526-89.291)	88.067 *** (81.682-94.452)	92.121 *** (85.731-98.512)	91.552 *** (85.159-97.945)
Asian	82.327 (75.671-88.984)	86.328 (79.673-92.983)	90.009 (83.347-96.671)	90.062 (83.403-96.721)
Log_{10} Peripheral vascular resistance				
White	3.167 (3.135-3.199)	3.131 (3.099-3.163)	3.117 (3.085-3.149)	3.139 (3.108-3.171)
Black	3.176 (3.144-3.209)	3.140 (3.107-3.173)	3.126 (3.094-3.159)	3.149 (3.116-3.182)
Asian	3.198 *** ++ (3.163-3.232)	3.162 *** ++ (3.127-3.196)	3.148 *** ++ (3.113-3.182)	3.170 *** ++ (3.136-3.205)

Log_{10} Mean arterial pressure				
White	1.979 (1.972-1.986)	1.967 (1.961-1.974)	1.966 (1.959-1.972)	1.978 (1.972-1.985)
Black	1.972 * (1.964-1.980)	1.958 ** (1.950-1.966)	1.951 *** (1.943-1.959)	1.960 *** (1.952-1.968)
Asian	1.973 (1.964-1.983)	1.962 (1.952-1.971)	1.953 ** (1.944-1.963)	1.967 ** (1.958-1.977)

Compared to White: *p<0.05, ** p<0.01, ***p<0.001;

Compared to Black: +p<0.05, ++p<0.01, +++p<0.001

Figure 1